Original Article

Long-term treatment results and prognostic factors of synchronous and metachronous squamous cell carcinoma of head and neck and esophagus

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Background: The purpose was to investigate the prognosis of patients with synchronous and metachronous squamous cell carcinoma of head and neck (HNSCC) and esophagus (ESCC), and to evaluate the prognostic factors of these patients.

Methods: A retrospective review was performed on 70 patients with synchronous and metachronous HNSCC and ESCC treated in our institution from January 2005 to December 2016. Kaplan-Meier method and Cox proportional hazard model were used to evaluate overall survival (OS) and determine the prognostic factors associated with survival outcomes.

Results: The 1-, 2- and 3-year OS rates were 77.1%, 57.1% and 37.1% with the median survival time for 33.5 months. The univariate analysis results revealed that the patients with early-stage of ESCC, metachronous cancer, and receiving surgery for both cancer had better OS (P=0.003; P=0.035; P=0.002). The multivariate analysis showed that the clinical stage of ESCC and receiving surgery for both cancer or not were the independent prognostic factors for OS.

Conclusions: The multidisciplinary treatment outcome is acceptable, especially for patients with early clinical stage ESCC and with chance to receiving surgery for both cancer.

Keywords: Synchronous cancer; metachronous cancer; squamous cell carcinoma of esophagus (ESCC); squamous cell carcinoma of head and neck (HNSCC); prognosis

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Introduction

Squamous cell carcinoma of head and neck (HNSCC) is one of the most common malignant tumors. About 7–20% of patients with HNSCC accompany by the second primary tumors of the upper digestive tract and respiratory tract synchronously or metachronously. Similarly, multiple primary cancers are frequently detected in squamous cell carcinoma of esophagus (ESCC). Many studies have reported that about 10–22% of patients with ESCC accompany by the second primary tumors such as stomach cancer, head and neck cancer, lung cancer, and etc. (1-3). In these ESCC patients with multiple primary cancer, HNSCC is the second most common malignancy (4-7). The high incidence of synchronous and metachronous HNSCC

and ESCC may attribute to the same epidemiological risk factors such as drinking, smoking, eating habits and so on (8-10). Lim *et al.* (11) found that tobacco and alcohol were the important pathogenic factors for such patients (P=0.028; P=0.019). In addition, the "regional carcinogenicity" theory also supports the view that the double primary HNSCC and ESCC is caused by exposure to the same carcinogenic substance (9,12). With the application of esophagoscopy supplemented with iodine staining and ^{18}F-FDG PET/CT, the detectable rate of ESCC in HNSCC patients, especially for early-stage disease, has an increasing trend in recent years (10,13,14). In addition, the improved survival after treatment for the first cancer also results in more frequent detection of the second cancer in these patients (15,16).

The treatment options for these patients are faced with pronounced difficulties, and the prognosis is relatively poor (17-21). In addition, the nature of its relative low incidence leads to the lack of high-grade evidence-based treatment consensus for these patients without large series clinical studies focusing on the treatment optimization. The main reason is that most of these diseases are complicated, and the following clinical factors, including the interval time between two kinds of cancer (synchronous or metachronous), the location and clinical stages of two different cancer (22-26), the previous treatment method of the first cancer and so on, need to be taken into consideration before determining the treatment strategy. So, it is very necessary to determine the appropriate treatment strategy through multidisciplinary team to improve the outcomes of these diseases. The currently accepted pattern of care for these patients is combined modality approaches based on surgery, radiotherapy and chemotherapy and/or molecular target therapy (22,27,28). To provide the further information, we retrospectively analyzed the treatment modalities and prognosis of patients with synchronous and metachronous HNSCC and ESCC in our institution. The present study included relative larger numbers of patients than before, and the treatment strategy of all patients was determined by the multidisciplinary team.

Methods

Patients characteristic

All patients with synchronous and metachronous HNSCC and ESCC receiving treatment in Fudan University Shanghai Cancer Center from January 2005 to December 2016 were recruited, except the patients with distant metastasis. Finally, 70 cases met the inclusion criteria. The clinical features, treatment information and outcome data were collected and analyzed through a retrospective review of medical records. According to differences in the interval time between two kinds of cancer, all patients were divided into synchronous group (time interval ≤6 months) and metachronous group (time interval >6 months). In metachronous group, there were 15 patients with ESCC followed by HNSCC and 34 patients with HNSCC followed by ESCC, respectively. The TNM staging systems (AJCC/UICC seventh edition) were used to stage the HNSCC and ESCC separately. The characteristics of all patients were shown in *Table 1*. There were 11 patients of oropharyngeal cancer, and only 4 patients were tested for p16 status. The expressions of p16 were negative in these 4 patients.

Treatment modalities

The treatment strategy of all patients was determined by the multidisciplinary team. The treatment modalities of all patients were shown in *Table 2*. For 21 patients with synchronous disease, 10 sites of HNSCC received surgery (3 receiving surgery through the peroral approach, 2 for partial laryngectomy and 5 for total oesopharyngolaryngectomy) and 7 received postoperative radiotherapy with or without chemotherapy. Other 11 sites of HNSCC received radiotherapy, and 7 patients also received chemotherapy and/or anti-EGFR target therapy. Sixteen sites of ESCC received surgery [8 receiving endoscopic submucosal dissection (ESD) or endoscopic mucosal resection (EMR), 3 for thoracotomy, 5 for total oesopharyngolaryngectomy] and 10 received postoperative radiotherapy with or without chemotherapy. Other 5 sites of ESCC received radiotherapy, and 2 patients also received chemotherapy.

There included 15 patients with ESCC followed by HNSCC and 34 patients with HNSCC followed by ESCC in 49 patients with metachronous disease, respectively. For 15 patients with ESCC followed by HNSCC, 10 sites of ESCC received surgery (6 receiving ESD or EMR, 4 for thoracotomy) and 5 received postoperative radiotherapy with or without chemotherapy. Other five sites of ESCC received radiotherapy, and 3 patients also received chemotherapy. Nine sites of HNSCC received surgery (2 receiving surgery through the peroral approach, 3 for partial laryngectomy, 3 for total laryngectomy, 1 for total pharyngolaryngectomy) and 6 patients received postoperative radiotherapy with or without chemotherapy, 5

Table 1 The clinical and pathological features of patients with HNSCC and ESCC

Parameters	Number	Percentage
Median age (year)	60 (range, 43–77)	
Median time interval between diagnosis of HNSCC and ESCC (months)	12.7 (range, 0–125.8)	
Sex		
Male	68	97.1
Female	2	2.9
Smoking		
Yes	45	64.3
No	25	35.7
Alcohol drinking		
Yes	40	57.1
No	30	42.9
The location of HNSCC		
Oral cavity	17	24.3
Oropharynx	11	15.7
Larynx	23	32.9
Hypopharynx	15	21.4
Multiple sites	4	5.7
The location of ESCC		
Cervical	8	11.4
Upper thoracic	14	20.0
Middle thoracic	27	38.6
Lower thoracic	13	18.6
Multiple sites	3	4.3
Unknown	5	7.1
Clinical stage of HNSCC		
Stage I	4	5.7
Stage II	8	11.4
Stage III	34	48.6
Stage IV	24	34.3
Clinical stage of ESCC		
Stage I	17	24.3
Stage II	13	18.6
Stage III	26	37.1
Stage IV	14	20.0
Occurrence sequence of cancer		
Synchronous disease	21	30.0
ESCC followed by HNSCC	15	21.4
HNSCC followed by ESCC	34	48.6

OS, overall survival; HNSCC, squamous cell carcinoma of head and neck; ESCC, squamous cell carcinoma of esophagus.

Table 2 The treatment modalities of patients with HNSCC and ESCC

The patient groups	Surgery ± radio(chemo) therapy	Radio(chemo) and/or target therapy	χ^2	P
Treatment of HNSCC				
Synchronous cancer	10 (47.6)	11 (52.4)		
ESCC followed by HNSCC	9 (60.0)	6 (40.0)	0.538	0.463
HNSCC followed by ESCC	27 (79.4)	7 (20.6)	5.960	0.015
Treatment of ESCC				
Synchronous cancer	16 (76.2)	5 (23.8)		
ESCC followed by HNSCC	10 (66.7)	5 (33.3)	0.396	0.529
HNSCC followed by ESCC	24 (70.6)	10 (29.4)	0.205	0.650

OS, overall survival; HNSCC, squamous cell carcinoma of head and neck; ESCC, squamous cell carcinoma of esophagus.

received neither radiotherapy nor chemotherapy and 6 were unknown. Other six sites of HNSCC received radiotherapy, and 4 patients also received chemotherapy and/or anti-EGFR target therapy.

For 34 patients with HNSCC followed by ESCC, 27 sites of HNSCC received surgery (4 receiving through the peroral approach, 6 for partial laryngectomy, 7 for total laryngectomy, 10 for total pharyngolaryngectomy) and 19 patients received postoperative radiotherapy with or without chemotherapy, 3 received neither radiotherapy nor chemotherapy and 5 were unknown. Other 7 sites of HNSCC received radiotherapy, and 5 patients also received chemotherapy and/or anti-EGFR target therapy. Twenty-four sites of ESCC received surgery (10 receiving ESD or EMR, 14 for thoracotomy) and 19 patients received postoperative radiotherapy with or without chemotherapy, 3 received neither radiotherapy nor chemotherapy and 2 were unknown. Other 10 sites of ESCC received radiotherapy, and 8 patients also received chemotherapy.

The statistical results showed that the ratio of receiving surgery for the sites of HNSCC in patients with HNSCC followed by ESCC was significantly higher than in patients with synchronous disease (*Table 2*).

Statistical analysis

All statistical analyses were performed by using SPSS version 19.0. Overall survival (OS) rate for these patients was calculated. The OS was defined from the diagnosis of second primary tumor to the last follow-up or the death from any cause. Kaplan-Meier method was used to evaluate OS, and log-rank test was used to analyze the difference in different groups. The univariate and multivariate analysis by Cox proportional hazard model were performed to determine the factors associated with survival outcomes. For all tests, a two-sided P<0.05 was considered to be significant.

Results

The treatment outcomes

The median follow-up time of all patients was 33.7 (0.5–130.0) months. Fifty-five patients had been confirmed dead until last follow-up. Among 55 deaths, 14 (25.5%) died of distant metastasis, 22 (40.0%) died of loco-regional recurrence (6 for esophagus and 16 for head and neck), 9 (16.4%) died of loco-regional recurrence with distant metastasis 4 (7.3%) died of other disease and 6 (10.9%) died of unknown reason. The 1-, 2- and 3-year OS rates were 77.1%, 57.1% and 37.1%, respectively (*Figure 1*). The median survival time of all patients was 33.5 months.

Prognostic factors

The Kaplan-Meier plots showed that the 3-year OS was significantly correlated with stage of ESCC (P=0.003), synchronous or metachronous cancer (P=0.035) and with or without receiving surgery for both cancer (P=0.002) (*Figure 2*; *Table 3*). The occurrence sequence of cancer and the clinical stages of both cancer were the variables suggesting a significant trend for OS (P=0.088; P=0.080). The patient age and clinical stage of HNSCC were not the significant variables (P=0.850; P=0.426) (*Table 3*). The

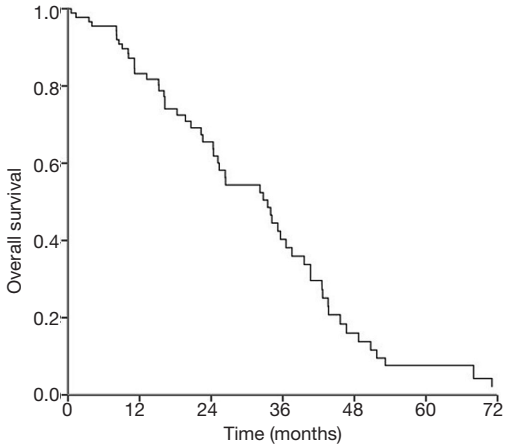

Figure 1 The Kaplan-Meier plots of OS for all patients with HNSCC and ESCC. OS, overall survival; HNSCC, squamous cell carcinoma of head and neck; ESCC, squamous cell carcinoma of esophagus.

multivariate analysis showed that the clinical stage of ESCC (P=0.011) and receiving surgery for both cancer or not were the independent prognostic factors for OS (*Table 4*).

Discussion

There has no consensus of treatment strategy for these patients until now. It is hard to decide whether to treat each cancer separately or not, whether to perform chemotherapy and/or radiation therapy, and whether to perform simultaneous or staged operations if operations are possible. The choice of treatment strategy should take into consideration the interval time between two kinds of cancer (synchronous or metachronous), the location and clinical stages of two different cancer, the previous treatment method of the first cancer, patient

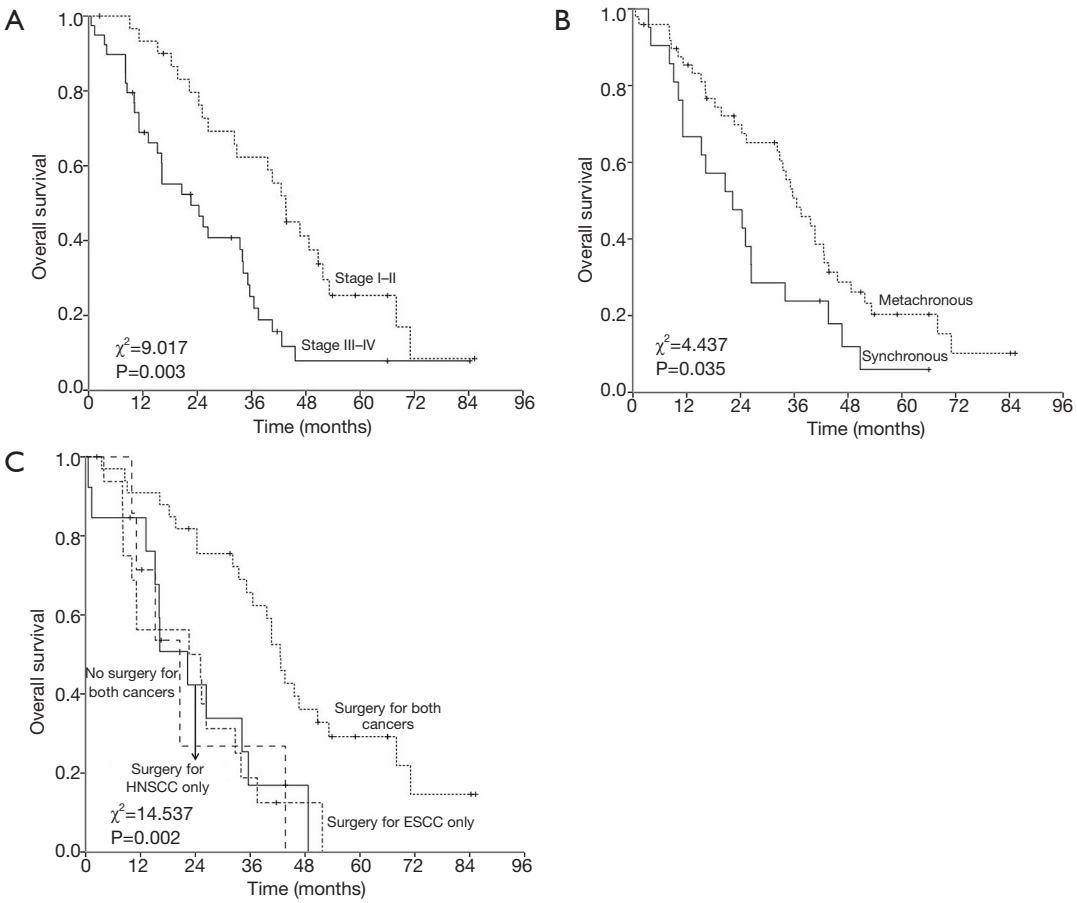

Figure 2 The Kaplan-Meier plots of OS for different groups in patients with HNSCC and ESCC: (A) the survival curves according to the clinical stages of ESCC; (B) the survival curves according to synchronous or metachronous groups; (C) the survival curves according to the treatment modalities. OS, overall survival; HNSCC, squamous cell carcinoma of head and neck; ESCC, squamous cell carcinoma of esophagus.

Table 3 Univariate analysis for OS in patients with HNSCC and ESCC

Variables	3-year OS	HR (95% CI)	χ^2	P
Age (year)				
≤60	41.3	0.950 (0.559–1.616)	0.036	0.850
>60	43.0			
Clinical stage of ESCC				
I–II	62.3	0.426 (0.244–0.743)	9.017	0.003
III–IV	25.1			
Clinical stage of HNSCC				
I–II	47.6	0.747(0.365–1.532)	0.633	0.426
III–IV	40.7			
Clinical stages of HNSCC and ESCC			5.044	0.080
Stage I–II for both cancer	66.7	0.345 (0.119–0.999)	3.850	0.050
Stage III–IV for one of cancer	53.5	0.640 (0.367–1.118)	2.459	0.117
Stage III–IV for both cancer	27.1			
Synchronous or metachronous cancer				
Synchronous	23.8	1.839 (1.043–3.241)	4.437	0.035
Metachronous	50.7			
Occurrence sequence of cancer			4.871	0.088
ESCC followed by HNSCC	70.0	0.450 (0.208–0.972)	4.131	0.052
HNSCC followed by ESCC	42.0	0.596 (0.325–1.094)	2.787	0.095
Synchronous disease	23.8			
Receiving surgery			14.537	0.002
Surgery for both cancer	65.7	0.320 (0.117–0.872)	4.956	0.026
Surgery for ESCC only	18.8	1.031 (0.370–2.869)	0.003	0.954
Surgery for HNSCC only	16.9	0.909 (0.314–2.635)	0.031	0.861
No surgery for both cancer	26.8			

OS, overall survival; HNSCC, squamous cell carcinoma of head and neck; ESCC, squamous cell carcinoma of esophagus.

conditions, and even the oncologist's expertise. Therefore, a multidisciplinary team management approach is essential for customized treatment strategies in these patients. The treatment strategy of all patients in present study were determined by the multidisciplinary team. Most of ESCC in these patients received surgery. We divided the patients into three groups: synchronous group, ESCC followed by HNSCC group and HNSCC followed by ESCC group, and found that there were no significant differences in percent of patients receiving surgery among these groups. It suggested that the possibility of receiving surgery for ESCC may not be affected whether or not synchronous or metachronous HNSCC existed (24). However, the possibility of receiving surgery for HNSCC may be affected by the existence of ESCC. The rate of receiving surgery for HNSCC in HNSCC followed by ESCC group is higher than in synchronous group. The main reason is that the synchronous cancer is complicated and the surgical indications of HNSCC are often more limited than for solitary HNSCC.

We reviewed previous published literature (*Table 5*), and found that the 2-year OS for these patients were 16.7–44.0%. Our results showed that the 1-, 2- and 3-year OS for these patients were 77.1%, 57.1% and 37.1%,

Table 4 Multivariate analysis for OS in patients with HNSCC and ESCC

Variables	HR (95% CI)	χ^2	P
Clinical stage of ESCC			
Stage I–II	0.470 (0.262–0.843)	6.416	0.011
Stage III–IV			
Synchronous or metachronous cancer			
Synchronous	1.564 (0.854–2.866)	2.098	0.147
Metachronous	–	–	–
Receiving surgery		12.131	0.007
Surgery for both cancer	0.303 (0.108–0.847)	5.183	0.023
Surgery for ESCC only	0.773 (0.272–2.200)	0.233	0.629
Surgery for HNSCC only	0.933 (0.315–2.764)	0.016	0.901
No surgery for both cancer	–	–	–

OS, overall survival; HNSCC, squamous cell carcinoma of head and neck; ESCC, squamous cell carcinoma of esophagus.

Table 5 The treatment results of synchronous and metachronous HNSCC and ESCC in previous published research and our study

Study	Patient number	Treatment method	PFS (%)		OS (%)			Median survival time (months)
			1-year	2-year	1-year	2-year	3-year	
Park (10)	27 (synchronous)	Surgery/radiotherapy/chemotherapy	–	57.5	–	39.6	–	28.2
Yoshino (17)	21 (metachronous)	Surgery/radiotherapy	–	–	–	42.0	30.0	–
Shinoto (18)	34 (synchronous)	Radiotherapy/chemotherapy	–	33.0	–	44.0	–	–
Lim (11)	37 (synchronous)	Surgery/radiotherapy/chemotherapy	–	–	–	–	48.2	–
	11 (metachronous)	Surgery/radiotherapy/chemotherapy	–	–	–	–	–	–
Welza (7)	24 (synchronous)	Surgery/radiotherapy/chemotherapy	–	–	–	–	–	37.0
Hsu (19)	12 (synchronous)	Radiotherapy/chemotherapy	–	–	41.7	16.7	–	10.3
Fan (20)	41 (synchronous)	Surgery/radiotherapy/chemotherapy	37.0	10.0	62.0	18.0	–	–
Present study	21 (synchronous)	Surgery/radiotherapy/chemotherapy	–	–	77.1	57.1	37.1	33.5
	49 (metachronous)	Surgery/radiotherapy/chemotherapy	–	–	–	–	–	–

OS, overall survival; PFS, progression-free survival; HNSCC, squamous cell carcinoma of head and neck; ESCC, squamous cell carcinoma of esophagus.

respectively, and the median survival time was 33.5 months. The multivariate analysis showed that the clinical stage of ESCC was one of the independent prognostic factors for OS while the clinical stage of HNSCC was not. Park *et al.* (10) also found that the long-term treatment results were closely related to the severity of ESCC, but not related to HNSCC. Shinoto *et al.* (18) found that the advanced clinical stage (III–IV) of ESCC was one of the unfavorable prognostic factors of OS for these patients with double primary cancer. The main reason may be that ESCC has a much poorer outcome than HNSCC, and the prognosis would generally be determined by the clinical stage of ESCC (10).

In present study, these patients were divided into four groups according to whether surgery is received or not: receiving surgery for both cancer, receiving surgery for ESCC only, receiving surgery for HNSCC only, and no receiving surgery for both cancer. We found that

the patients with receiving surgery for both cancer had better OS compared to the other patients. Multivariate analysis showed that it was the independent prognostic factor for OS. This result is similar to the previous studies (22,23,27,28). Furthermore, univariate analysis revealed that the 3-year OS of patients with metachronous cancer was higher than the patients with synchronous cancer (50.7% *vs.* 23.8%, P=0.035). The main reason may be that the synchronous cancer is more complicated and serious than the metachronous cancer. It means that the patients with metachronous cancer have more opportunities to receive aggressive treatment than the patients with synchronous cancer. Our study revealed that there were no significant differences in rates of ESCC receiving surgery among different groups. However, the rate of HNSCC receiving surgery in metachronous group is higher than in synchronous group.

In conclusion, our results suggested that the treatment outcome of patients with synchronous or metachronous HNSCC and ESCC was acceptable, especially for patients with early clinical stage ESCC and with chance to receiving surgery for both cancer. It is very necessary to determine the appropriate treatment strategy through multidisciplinary team to improve the outcomes of these diseases. However, this retrospective study is potentially limited by the relatively small number of patients, and it was very difficult to analyze the effect of different treatment strategies on prognosis according to tumor sites of HNSCC and ESCC.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr.2019.12.81). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by Fudan University Shanghai Cancer Center (No. 1905202-11). Informed consent was waived.

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